PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	02 JUN 2008
Applicant's or agent's file reference 76806-PCT/JPW/BB	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/02471	25 February 2008 (25.02.2008)	26 February 2007 (26.02.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 35/00; A61K 31/12 (2008.04)
USPC - 514/679

Applicant TEVA PHARMACEUTICAL INDUSTRIES, LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	13 May 2008 (13.05.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 5-21

because: Improper multiple dependant claims

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-21 are so unclear that no meaningful opinion could be formed *(specify)*:
Claims 5-21 are improper multiple dependent claims.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 5-21

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-4 and 23	YES
	Claims	22	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-4, 22 and 23	NO
Industrial applicability (IA)	Claims	1-4, 22 and 23	YES
	Claims	None	NO

2. Citations and explanations:

Claim 22 lacks novelty under PCT Article 33(2) as being anticipated by 2006/0173053 A1 Shinitzsky et al. (hereinafter "Shinitzsky").

Regarding claim 22, Shinitzsky teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier (para [0122] - "The pharmaceutical composition...may further include...pharmaceutically acceptable..carriers...") and a compound of the formula (para [0059]), wherein
R.sub.1 is C.sub.10-C.sub.24 is alkenyl (para [0060] - "R.sub.1 is...C.sub.10-C.sub.24 alkenyl");
R.sub.2 is H, C.sub.1-C.sub.6 alkyl, aryl, or aralkyl, where any aryl
moiety may be unsubstituted or substituted by nitro, cyano, halo, hydroxyl, NR.sub.6R.sub.7, or CR.sub.8R.sub.8NR.sub.6R.sub.7, where R.sub.6, R.sub.7 and R.sub.8 each independently is H or C.sub.1-C.sub.6 alkyl; (para [0062] - "wherein R.sub.2 is H, C.sub.1-C.sub.6 alkyl, aryl, or aralkyl, wherein any aryl moiety may be unsubstituted or substituted by nitro, cyano, halo, hydroxy, NR.sub.6R.sub.7 or CR.sub.8R.sub.8NR.sub.6R.sub.7; and
R.sub.3 and R.sub.4 each independently is H or C.sub.1-C.sub.6 alkyl (para [0062] - "R.sub.3 is H...or C.sub.1-C.sub.6 alkyl..."), or R.sub.3 and R.sub4 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic saturated ring (para [0063]) optionally containing an additional N or O, which is unsubstituted or substituted by C.sub.1-C.sub.6 alkyl, or an enantiomer (para [0115]) or a pharmaceutically acceptable salt of the compound (para [0109]), in an amount effective to treat the subject (para [0124] - "...administering to a patient in need an effective amount of a compound of formula I as defined hereinbefore.").

Claims 1-4 and 23 lack an inventive step under PCT Article 33(3) as being obvious over Shinitzsky.

Regarding claim 1, Shinitzsky teaches a method of treating a subject afflicted with an autoimmune, inflammatory diseases associated with graft rejection (para [0117] - "Inflammatory disease, disorders or conditions that can be treated with the immunomodulators of the present invention include...an inflammation associated with...a condition selected from graft rejection.") by "activat{ing} T cells for the purposes of therapy of autoimmune diseases and for T-cell mediated immune effects that need preferably a T.sub.H.sup.2-type immune response" (para [0047]), comprising administering to the subject a compound having the formula (para [0059]), wherein
R.sub.1 is C.sub.10-C.sub.24 is alkenyl (para [0060] - "R.sub.1 is...C.sub.10-C.sub.24 alkenyl");
R.sub.2 is H, C.sub.1-C.sub.6 alkyl, aryl, or aralkyl, where any aryl
moiety may be unsubstituted or substituted by nitro, cyano, halo, hydroxyl, NR.sub.6R.sub.7, or CR.sub.8R.sub.8NR.sub.6R.sub.7, where R.sub.6, R.sub.7 and R.sub.8 each independently is H or C.sub.1-C.sub.6 alkyl; (para [0062] - "wherein R.sub.2 is H, C.sub.1-C.sub.6 alkyl, aryl, or aralkyl, wherein any aryl moiety may be unsubstituted or substituted by nitro, cyano, halo, hydroxy, NR.sub.6R.sub.7 or CR.sub.8R.sub.8NR.sub.6R.sub.7; and
R.sub.3 and R.sub.4 each independently is H or C.sub.1-C.sub.6 alkyl (para [0062] - "R.sub.3 is H...or C.sub.1-C.sub.6 alkyl..."), or R.sub.3 and R.sub4 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic saturated ring (para [0063]) optionally containing an additional N or O, which is unsubstituted or substituted by C.sub.1-C.sub.6 alkyl, or an enantiomer (para [0115]) or a pharmaceutically acceptable salt of the compound (para [0109]), in an amount effective to treat the subject (para [0124] - "...administering to a patient in need an effective amount of a compound of formula I as defined hereinbefore."). However, Shinitzsky does not specifically disclose a method of treating a subject afflicted with alopecia areata. Since Shinitzsky teaches that esters of aminoacetic acid with long chain alcohols have been employed in hair cosmetics (para [0036]), and alopecia areata is well known in the art to be an autoimmune disease that responds to treatment with immunomodulating agents, it would have been obvious to one of ordinary skill in the art to treat the subject afflicted with alopecia areata by administering to the subject the compound of said formula.

Continued

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V(2): Citations and explanations

Regarding claim 2, Shinitzsky teaches
R.sub.1 that is C.sub.16-C.sub.20 (para [0097] - "alpha-Amino-alpha-phenyl-acetic acid octadec-(Z)-9-enyl ester HCl salt.");
R.sub.2 that is aryl, or aralkyl (para [0097] - "alpha-Amino-alpha-phenyl-acetic acid octadec-(Z)-9-enyl ester HCl salt.");
R.sub.3 and R.sub.4 that are each H, or R.sub.3 and R.sub.4 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic saturated ring optionally containing an additional N or O, which is unsubstituted or substituted by C.sub.1-C.sub.6 alkyl, or an enantiomer or pharmaceutically acceptable salt of the compound (para [0097] - "alpha-Amino-alpha-phenyl-acetic acid octadec -(Z)-9-enyl ester HCl salt.").

Regarding claim 3, Shinitzsky teaches R.sub.1 that is C.sub.18 alkenyl (para [0097] - "alpha-Amino-alpha-phenyl-acetic acid octadec-(Z)-9 -enyl ester HCl salt.").

Regarding claim 4, Shinitzsky teaches R.sub.1 that is cis-9-octadecanyl (para [0097] - "alpha-Amino-alpha-phenyl-acetic acid octadec-(Z)-9-enyl ester HCl salt.").

Regarding claim 23, Shinitzsky teaches the use of the compound having the formula, wherein
R.sub.1 is C.sub.10-C.sub.24 is alkenyl (para [0060] - "R.sub.1 is...C.sub.10-C.sub.24 alkenyl");
R.sub.2 is H, C.sub.1-C.sub.6 alkyl, aryl, or aralkyl, where any aryl moiety may be unsubstituted or substituted by nitro, cyano, halo, hydroxyl, NR.sub.6R.sub.7, or CR.sub.8R.sub.8NR.sub.6R.sub.7, where R.sub.6, R.sub.7 and R.sub.8 each independently is H or C.sub.1-C.sub.6 alkyl; (para [0062] - "wherein R.sub.2 is H, C.sub.1-C.sub.6 alkyl, aryl, or aralkyl, wherein any aryl moiety may be unsubstituted or substituted by nitro, cyano, halo, hydroxy, NR.sub.6R.sub.7 or CR.sub.8R.sub.8NR.sub.6R.sub.7; and
R.sub.3 and R.sub.4 each independently is H or C.sub.1-C.sub.6 alkyl (para [0062] - "R.sub.3 is H...or C.sub.1-C.sub.6 alkyl..."), or R.sub.3 and R.sub4 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic saturated ring (para [0063]) optionally containing an additional N or O, which is unsubstituted or substituted by C.sub.1-C.sub.6 alkyl, or an enantiomer (para [0115]) or a pharmaceutically acceptable salt of the compound (para [0109]), in an amount effective to treat the subject (para [0124] - "...administering to a patient in need an effective amount of a compound of formula I as defined hereinbefore.") or of an enantiomer of the compound, or of a pharmaceutically acceptable salt of the compound, for the preparation of a medicament for the treatment of alopecia areata in an afflicted subject - see the above argument for claim 1.

Claims 1-4, 22 and 23 have industrial applicability as defined by PCT Article 33(4), because the subject matter can be made or used in the industry.